What is claimed is:

1. A copolymer composition comprising semi-random sequence copolymers having at least two fixed anchor residues which are separated by 7 amino acid residues, wherein:

(1) the anchor residue is selected from aspartic acid residue (D) and glutamic acid residue (E);

(2) the remainder of the copolymer has a random sequence comprising at least two amino acid residues, one amino acid selected from each amino acid residue group

(a) alanine (A) or glycine (G); and

(b) leucine (L), isoleucine (I), valine (V), methionine (M), threonine (T), serine (S), and cysteine (C);

optionally further comprising proline (P).

2. A copolymer composition comprising random-sequence copolymers the amino acid composition of which comprises at least four different amino acid residues, wherein at least one amino acid residue is selected from each of the group consisting of:

(1) glutamic acid (E), aspartic acid (D);

(2) leucine (L), isoleucine (I), valine (V), and methionine (M);

(3) threonine (T), serine (S), and cysteine (C); and

(4) alanine (A) and glycine (G);

optionally further comprising proline (P).

3. The copolymer composition of claim 2, wherein the copolymer is a tetrapolymer having an amino acid composition selected from:

(1) aspartic acid, alanine, leucine, glutamic acid (DALE);

(2) aspartic acid, alanine, isoleucine, glutamic acid (DAIE);

(3) aspartic acid, alanine, valine, glutamic acid (DAVE);

(4) aspartic acid, alanine, threonine, glutamic acid (DATE); and

(5) aspartic acid, alanine, serine, glutamic acid (DASE).

BEST AVAILABLE COPY

4. The copolymer composition of claim 2, wherein the copolymer is a tetrapolymer having an amino acid composition selected from:

(1) aspartic acid, glycine, leucine, glutamic acid (DGLE);

(2) aspartic acid, glycine, isoleucine, glutamic acid (DGIE);

(3) aspartic acid, glycine, valine, glutamic acid (DGVE);

(4) aspartic acid, glycine, threonine, glutamic acid (DGTE); and

(5) aspartic acid, glycine, serine, glutamic acid (DGSE).

5. A copolymer composition comprising amino acid residues:

(1) aspartic acid, alanine, leucine, and glutamic acid (DALE);

(2) aspartic acid, alanine, isoleucine, and glutamic acid (DAIE);

(3) aspartic acid, alanine, valine, and glutamic acid (DAVE); or

(4) aspartic acid, alanine, threonine, and glutamic acid (DATE);

in a random sequence.

6. A copolymer composition comprising amino acid residues:

(1) aspartic acid, glycine, leucine, and glutamic acid (DGLE);

(2) aspartic acid, glycine, isoleucine, and glutamic acid (DGIE);

(3) aspartic acid, glycine, valine, and glutamic acid (DGVE); or

(4) aspartic acid, glycine, threonine, and glutamic acid (DGTE)

in a random sequence.

7. The copolymer composition of claim 3 or 4, wherein the molar output ratio of amino acid residues D:A:X:E or D:G:X:E, wherein X is L, I, V, S, or T, is about:

(1) 1:10:3:1;

(2) 1:15:3:1;

(3) 1:25:15:5; or

(4) 1:3:1.5:0.2;

wherein the variability in the molar output ratios comprises a range of about 10% between the different amino acids.

8. The copolymer composition of claim 5 or 6, wherein the molar output ratio of amino acid residues D:A:X:E or D:G:X:E, wherein X is L, I, V, or T, is about:

(1) 1:10:3:1;

(2) 1:15:3:1;

(3) 1:25:15:5; or

(4) 1:3:1.5:0.2;

wherein the variability in the molar output ratios comprises a range of about 10% between the different amino acids.

9. The copolymer composition of claim 3 or 4, wherein the molar input ratio of amino acid residues D:A:X:E or D:G:X:E, wherein X is L, I, V, S, or T, is about:

(1) 1:5:3:1;

(2) 1:25:15:5; or

(3) 1:1:1.5:0.2.

10. The copolymer composition of claim 5 or 6, wherein the molar input ratio of amino acid residues D:A:X:E or D:G:X:E, wherein X is L, I, V, or T, is about:

(1) 1:5:3:1;

(2) 1:25:15:5; or

(3) 1:1:1.5:0.2.

11. The copolymer composition of claim 3 or 4, wherein the copolymer further comprises an additional amino acid residue which is found in an autoantigenic peptide specific for a HLA-DQ protein.

12. The copolymer composition of claim 11, wherein the additional amino acid residue is a lysine residue (K).

13. The copolymer composition of any of claims 1 to 12, wherein the copolymer functionally binds to an MHC protein HLA-DQ.

14. The copolymer composition of any of claims 1 to 13, wherein the copolymer comprises 30 to 70 amino acid residues.

15. The copolymer composition of claim 14, wherein the copolymer comprises about 50 amino acid residues.

16. The copolymer composition according to any of claims 1 to 15, wherein the copolymer is synthesized by solid phase chemistry.

17. A copolymer composition comprising random- or semi-random sequence copolymers having at least three different amino acid residues, wherein at least one amino acid residue is aspartic acid residue or glutamic acid residue, wherein the copolymers functionally bind to a class II MHC protein HLA-DQ.

18. The copolymer composition of claim 13, wherein the HLA-DQ is associated with an autoimmune disease.

19. The copolymer composition of claim 18, wherein the autoimmune disease is insulin-dependent diabetes mellitus or celiac disease.

20. The copolymer composition of claim 13, wherein the HLA-DQ is associated with an unwanted immune response.

21. The copolymer composition of claim 13, wherein the HLA-DQ is associated with an allergy.

22. The copolymer composition of claim13, wherein the HLA-DQ is associated with a disease treatable by administering the copolymer composition.

23. The copolymer composition of claim 13, wherein the HLA-DQ is HLA-DQ2 (a combination of alleles DQA1*0501-DQB1*0201) or HLA-DQ8 (a combination of alleles DQA1*03-DQB1*0302).

24. A pharmaceutical composition for treatment of an autoimmune disease, comprising a pharmaceutically effective amount of a copolymer composition comprising copolymers that functionally bind to an HLA-DQ molecule

associated with the autoimmune disease, and a pharmaceutically acceptable carrier and/or an excipient.

25. The pharmaceutical composition of claim 24, wherein the copolymer composition is the copolymer composition of claim 18.

26. The pharmaceutical composition of claim 25, further comprising an additional therapeutically active agent.

27. The pharmaceutical composition of claim 26, wherein the additional therapeutically active agent is a second copolymer composition that binds to a second HLA molecule associated with the autoimmune disease.

28. The pharmaceutical composition of claim 27, wherein the second HLA molecule is a HLA-DQ molecule.

29. The pharmaceutical composition of claim 27, wherein the second HLA molecule is a HLA-DR molecule.

30. The pharmaceutical composition of any of claim 24 to 29, wherein the autoimmune disease is a diabetic condition or celiac disease.

31. The pharmaceutical composition of claim 26, wherein the additional therapeutically active agent is insulin.

32. The pharmaceutical composition of claim 26, wherein the additional therapeutically active agent is one or more immunosuppressants.

33. The pharmaceutical composition of claim 32, wherein the immunosuppressant is

(1) a drug, selected from: rapamycin; a corticosteroid; an azathioprine; mycophenolate mofetil; a cyclosporine; a cyclophosphamide; a methotrexate; a 6-mercaptopurine; FK506; 15-deoxyspergualin; a sphingosine-1-phosphate (S1P) agonist; FTY 720 (2-amino-1,3-propanediol; a 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol

hydrochloride); a mitoxantrone; a 6-(3-dimethyl-aminopropionyl) forskolin; and a demethimmunomycin; or

(2) a protein, selected from: hul 124; BTI-322; allotrap-HLA-B270; OKT4A; Enlimomab; ABX-CBL; OKT3; ATGAM; basiliximab; daclizumab; thymoglobulin; ISAtx247; Medi-500; Medi-507; Alefacept; efalizumab; infliximab; and an interferon.

34. A pharmaceutical composition for treatment of an unwanted immune response, comprising a pharmaceutically effective amount of a copolymer composition comprising copolymers that functionally bind to an HLA-DQ molecule associated with the unwanted immune response, and a pharmaceutically acceptable carrier and/or an excipient.

35. The pharmaceutical composition of claim 34, wherein the copolymer composition is the copolymer composition of claim 20.

36. A pharmaceutical composition for treatment of an allergy, comprising a pharmaceutically effective amount of a copolymer composition comprising copolymers that functionally bind to an HLA-DQ molecule associated with the allergy, and a pharmaceutically acceptable carrier and/or an excipient.

37. The pharmaceutical composition of claim 36, wherein the copolymer composition is the copolymer composition of claim 21.

38. A pharmaceutical composition for treatment of a disease treatable by administering a copolymer composition, comprising a pharmaceutically effective amount of the copolymer composition comprising copolymers that functionally bind to an HLA-DQ molecule associated with the disease treatable by administering the copolymer composition, and a pharmaceutically acceptable carrier and/or an excipient.

39. The pharmaceutical composition of claim 37, wherein the copolymer composition is the copolymer composition of claim 22.

40. A method for treating an autoimmune disease comprising administering to a subject having the autoimmune disease a therapeutically effective amount of a copolymer composition that comprises one or more random sequence copolymers that binds to an HLA-DQ molecule associated with the autoimmune disease.

41. The method of claim 40, wherein said copolymer composition is a copolymer composition of claim 18.

42. The method of claim 41, further comprising administering a second therapeutically active agent.

43. The method of claim 42, wherein the second therapeutically active agent is a second copolymer composition that binds to a second HLA molecule associated with said autoimmune disease.

44. The method of claim 43, wherein said second HLA molecule is an HLA-DQ molecule.

45. The method of claim 43, wherein said second HLA molecule is an HLA-DR molecule.

46. The method of any of claims 40 to 45, wherein said autoimmune disease is selected from diabetic condition and celiac disease.

47. The method according to claim 46, wherein the diabetic condition is selected from: pre-diabetes, insulin-dependent diabetes mellitus (type I), and type II diabetes.

48. The method according to claim 46, wherein the diabetic condition is insulin-dependent diabetes mellitus (type I).

49. The method according to any of claim 40 to 48, wherein administering the copolymer is providing the copolymer by injection.

50. The method according to claim 49, wherein the locus of injection is selected from: intravenous (i.v.), subcutaneous (s.c.), intramuscular (i.m.), and intraperitoneal (i.p.).

51. The method according to claim 49, wherein administering the copolymer is providing an intravenous infusion.

52. The method according to claim 46, further comprising, after administering copolymer, observing a physiological parameter of the diabetic condition or celiac disease.

53. The method according to claim 52, wherein the parameter is decreased free blood glucose, increased blood insulin, increased pancreatic insulin, increased pancreatic mass, and increased number of beta islet cells.

54. The method according to claim 46, further comprising after administering copolymer, observing a decrease in frequency of diabetic episodes or decrease in severity of diabetic episodes.

55. The method according to claim 42, wherein the agent is insulin.

56. The method according to claim 55, wherein the amount of insulin to be administered is less than for the subject prior to administering the copolymer.

57. The method according to claim 42, wherein the agent is an immune suppressive agent.

58. The method according to claim 56, wherein the agent is:

(1) a drug, selected from: rapamycin; a corticosteroid; an azathioprine; mycophenolate mofetil; a cyclosporine; a cyclophosphamide; a methotrexate; a 6-mercaptopurine; FK506; 15-deoxyspergualin; a sphongosine-1-phosphate agonist; FTY 720 (2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride); a mitoxantrone; a 2-amino-1,3-propanediol; a 6-(3-dimethyl-aminopropionyl) forskolin; and a demethimmunomycin; or

(2) a protein, selected from: hul 124; BTI-322; allotrap-HLA-B270; OKT4A; Enlimomab; ABX-CBL; OKT3; ATGAM; basiliximab; daclizumab; thymoglobulin; ISAtx247; Medi-500; Medi-507; Alefacept; efalizumab; infliximab; and an interferon.

59. The method of any of claims 40 to 58, wherein the subject is a human.

60. The method of any of claims 40 to 58, wherein the subject is a rodent.

61. The method according to claim 60, wherein the subject is a non-obese diabetic (NOD) mouse or a streptozoticin-induced diabetic mouse.

62. A method for treating an unwanted immune response comprising administering to a subject having an unwanted immune response a therapeutically effective amount of a copolymer composition that comprises one or more random sequence copolymers that binds to an HLA-DQ molecule associated with the unwanted immune response.

63. The method of claim 62, wherein said copolymer composition is a copolymer composition of claim 20.

64. A method for treating an allergy comprising administering to a subject having a symptom of allergy a therapeutically effective amount of a copolymer composition that comprises one or more random sequence copolymers that binds to an HLA-DQ molecule associated with the allergy.

65. The method of claim 64, wherein said copolymer composition is a copolymer composition of claim 21.

66. A method for treating a disease treatable by administering a copolymer composition, comprising administering to a subject having the disease a therapeutically effective amount of a copolymer composition that comprises one or more random sequence copolymers that binds to an HLA-DQ molecule associated with the disease.

67. The method of claim 66, wherein said copolymer composition is a copolymer composition of claim 22.

68. A method for prophylactically treating a subject at risk of developing an autoimmune disease, comprising administering the copolymer of claim 18, wherein the onset of the autoimmune disease is delayed or prevented.

69. The method of claim 68, further comprising a second copolymer that binds to a second HLA molecule associated with said autoimmune disease.

70. The method of claim 69, wherein said second HLA molecule is a HLA-DQ molecule.

71. The method of claim 69, wherein said second HLA molecule is a HLA-DR molecule.

72. The method of any of claims 68 to 71, wherein said autoimmune disease is selected from type I diabetes mellitus and celiac disease.

73. A method of preventing progression of diabetes in a subject having a pre-diabetic condition, the method comprising administering to the subject a composition according to any of claims 1-18 and 25-33, thereby preventing progression of the diabetes.

74. The method according to claim 73, wherein the subject or family members of the subject have high blood glucose or high auto-antibody levels, compared to a control subject that does not have the condition.

75. A method of treating a subject recipient of pancreatic islet transplantation, the method comprising administering to the subject a composition according to any of claims 1-18 and 25-33.

76. The method according to claim 75, wherein administering the composition is prior to the islet transplantation.

77. The method according to claim 75, wherein administering the composition is subsequent to the islet transplantation.

78. The method according to any of claims 73 to 77, further comprising observing a physiological parameter in the subject.

79. The method according to claim 78, wherein the parameter is selected from the group of free blood glucose, blood insulin, pancreatic insulin, pancreatic mass, and number of beta islet cells.

80. A method for prophylactically treating a subject at risk of developing an unwanted immune response, comprising administering the copolymer of claim 19, wherein the onset of the unwanted immune response is delayed or prevented.

81. A method for prophylactically treating a subject at risk of developing an allergy, comprising administering the copolymer of claim 21, wherein the onset of the allergic reaction is delayed or prevented.

82. A method for prophylactically treating a subject at risk of developing disease treatable by administering the copolymer of claim 22, by administering the copolymer, wherein the onset of the unwanted immune response is delayed or prevented.

83. A method for identifying a copolymer that is therapeutically effective to treat an HLA-DQ mediated autoimmune disease comprising:

(a) synthesizing a random copolymer of amino acids selected from:

(1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine)

(2) acidic residues (aspartic acid, glutamic acid)

(3) small hydrophilic residues (serine, cysteine, threonine)

(4) small aliphatic residues (alanine, glycine)

and

(5) proline.

(b) determining binding of said copolymer to an HLA-DQ molecule;

(c) comparing binding of said copolymer to said HLA-DQ molecule with binding of a known autoantigenic peptide to said HLA-DQ;

(d) selecting said copolymer which binds to said HLA-DQ molecule substantially more strongly than said known autoantigenic peptide; and

(e) determining activation of T-helper cells moderated by said HLA-DQ molecule presenting said copolymer.

84. The method of claim 83, wherein said autoantigenic peptide is selected from:

(1) a peptide comprising amino acid residues 9-23 of human insulin;

(2) a peptide comprising amino acid residues 206-220 of human GAD; and

(3) a peptide comprising amino acid residues 441-460 of human HSP60.

85. The method of claim 84, wherein said HLA-DQ molecule is selected from DQA1*03-DQB1*0302, DQA1*0501-DQB1*0201, a trans dimer between HLA-DQA1*0501-DQB1*0201 and HLA-DQA1*03-DQB1*0302, DQA1*03/B1*0302, DQB1*0201/DQA1*0501, DQB1 *0201 and DQA1*03.

86. The method of any of claims 83 to 85, wherein the copolymer is biotinylated.

87. The method of any of claims 83 to 85, wherein the copolymer is labeled with FITC.

88. The method of any of claims 83 to 87, wherein the copolymer is capable of binding to class II MHC mouse protein IAg7.

89. A method of manufacture of a medicament for treatment of an autoimmune disease, comprising formulating the copolymer composition of any of claims 1 to 23 for administering to a subject with the autoimmune disease.

90. A method of manufacture of a medicament for treatment of insulin-dependent diabetes mellitus (IDDM) or celiac disease, comprising formulating the copolymer composition of claim 19 for administering to a subject with IDDM or celiac disease.

91. A method of manufacture of a medicament for treatment of unwanted immune response, comprising formulating the copolymer composition of claim 20 for administering to a subject with the unwanted immune response.

92. A method of manufacture of a medicament for treatment of an allergy, comprising formulating the copolymer composition of claim 21 for administering to a subject with the allergy.

93. A method of manufacture of a medicament for treatment of a disease treatable by administering the copolymer composition of claim 22, comprising formulating the copolymer composition for administering to a subject with the disease.

94. A kit for treating a diabetic subject comprising a copolymer having a random sequence of amino acids according to any of claims 5, 6, 8, 10, or 19 and a container.

95. The kit of claim 94, further comprising instructions for use.

96. The kit of claim 94, in a unit dose.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☑ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.